434

Treatment With Methylnaltrexone in Patients With Opioid-Induced Constipation With or Without Active Cancer

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INTRODUCTION

- Opioid-induced constipation (OIC) is a common side effect of opioid treatment and can affect the majority of patients on chronic opioid therapy, whether for cancer or noncancer pain[1-4]
- Treatment with laxatives or stool softeners can be administered, but these agents do not counteract the underlying mechanism in which opioids attach to peripheral μ-opioid receptors in the gastrointestinal tract; this may account for the limited effectiveness of these treatments[1,5]
- Unlike tolerance to analgesic effects, patients do not typically develop tolerance to OIC[5]
  - As a consequence, patients may take lower doses or discontinue opioid use altogether, compromising pain management[1]
- Attachment of opioids to peripheral μ-opioid receptors in the gastrointestinal tract leads to reduced gastrointestinal motility, inhibition of peristalsis, and prolongation of transit time[6]
  - Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, a Division of Bausch Health, Bridgewater, NJ, US) is a selective, peripherally acting μ-receptor antagonist that is restricted from crossing the blood-brain barrier and specifically decreases the constipating effect of opioid therapy without impacting opioid analgesia[6-9]
- MNTX tablets and subcutaneous (SC) injections are approved for the treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation[6]
- MNTX SC injection is approved for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care[6]
- The objective of this post hoc analysis of 3 randomized placebo-controlled trials (study 301 [NCT00401362], study 302 [NCT00402038], and study 4000 [NCT00672477]) was to assess potential differences in the efficacy of MNTX for OIC after the first dose among patients with or without active cancer who were receiving opioid therapy for pain, the majority of whom had not had an adequate response to conventional laxatives

METHODS

Key Inclusion Criteria

- Men and women aged ≥18 years
- Diagnosis of advanced illness (ie, terminal illnesses such as incurable cancer, end-stage diseases) with a life expectancy of ≥1 month (studies 302 and 4000) or 1 to 6 months (study 301)
- Receiving opioids routinely for discomfort or pain management for ≥3 days (study 301) or ≥2 weeks (studies 302 and 4000), excluding as-needed or rescue doses, and taking a stable regimen for ≥3 days before receiving the first dose of study medication
  - A stable regimen was defined as one with no reduction in opioid dose of ≥50% within 3 days prior to study drug administration
- OIC was defined as either of the following:
  - <3 bowel movements during the previous week and no clinically significant laxation in the 24 hours before the first dose of study drug (studies 4000 and 302 only)
  - No clinically significant laxation within 48 hours before the first dose of study drug
- Receiving a stable laxative regimen (eg, stool softener and senna or equivalent) for ≥3 days prior to the first dose of study drug

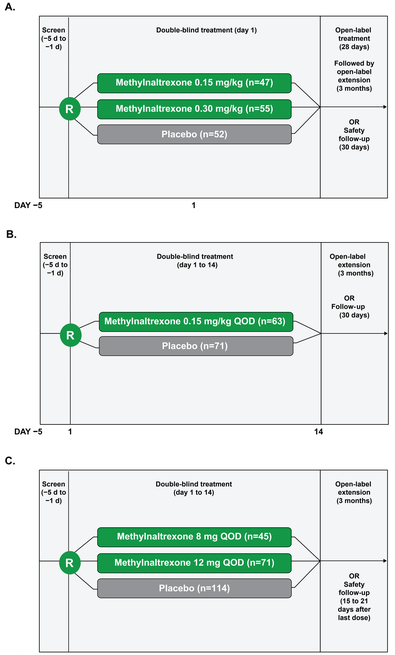
Key Exclusion Criteria

- History of MNTX treatment
- Any disease process suggestive of mechanical bowel obstruction
- Evidence of fecal impaction
- Any potential nonopioid cause of bowel dysfunction, in the opinion of the investigator
- History of fecal ostomy

Study Design

- This post hoc analysis included 3 multicenter, double-blind, randomized, placebo-controlled studies in adult patients with advanced illness and OIC
- In study 301, following a 5-day screening period, patients were randomized 1:1:1 to receive a single SC injection of MNTX 0.15 mg/kg, MNTX 0.30 mg/kg, or placebo (Figure 1A)
- In study 302, patients were randomized to receive SC injections of MNTX 0.15 mg/kg or placebo every other day for 2 weeks (Figure 1B). The dose could be adjusted up to 0.30 mg/kg beginning on day 9
- In study 4000, the dose of MNTX was determined by weight (Figure 1C)
  - Patients weighing 38 kg to <62 kg were randomized to receive SC injections of MNTX 8 mg or placebo every other day
  - Patients weighing ≥62 kg received MNTX 12 mg or placebo every other day for 14 days (a maximum of 7 doses)
- Patients were stratified post hoc into cancer and noncancer groups

Figure 1. Study Design for (A) Study 301, (B) Study 302, and (C) Study 4000



QOD = every other day; R = randomization.

Assessments

- Baseline characteristics of cancer and noncancer patients
- Efficacy endpoints after the first dose included laxation response at 4 and 24 hours postdose, rescue-free laxation (RFL) within ≤4 or ≤24 hours (RFL was defined as laxation without use of other laxative, enema, or suppository), and time to RFL
- Changes in pain score from baseline (both current pain and worst pain since baseline) were measured using a rating scale of 0 (no pain) to 10 (worst possible pain)
  - Changes in pain score were assessed at 4 hours postbaseline in study 301 and at 24 hours postbaseline in studies 302 and 4000
- Treatment-emergent adverse events were recorded from the safety population

Statistical Analyses

- Pooled patient data from the 3 studies were stratified by patients with active cancer and patients without cancer
- Baseline characteristics of cancer and noncancer patients were assessed using descriptive statistics
- Efficacy analyses were performed on the intent-to-treat (ITT) analysis set, which was defined as all patients who received ≥1 dose of study drug
- Statistical analysis included Chi-square tests for RFL response, Kaplan-Meier estimates for time to first RFL, and the t-test for pain scores difference from baseline
- Nominal levels of significance were set at 0.05, with no adjustment made for multiplicity

RESULTS

Patients

- The pooled study intent-to-treat population from the 3 studies included 355 patients with cancer and 163 patients without active cancer. Table 1 shows the baseline characteristics of the patients in the safety population (n=518)
- The median baseline opioid dose at baseline for patients with cancer (MNTX: 190 mg/d, n=198; placebo: 200 mg/d, n=157) was higher than that for patients without cancer (MNTX: 120 mg/d, n=82; placebo: 80 mg/d, n=80)
- There was no difference between the cancer and noncancer groups in pain scores or use of laxatives

Table 1. Baseline Characteristics Stratified by the Presence of Cancer in Patients (Pooled Safety Population)

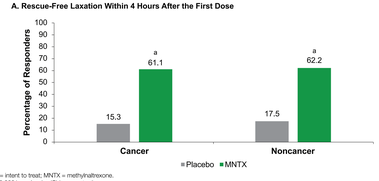
	Cancer Patients		Noncancer Patients	
Characteristic	**Placebo (n=157)**	**MNTX (n=198)**	**Placebo (n=80)**	**MNTX (n=83)**
Age, years				
Mean (range)	63.9 (21.0–100.0)	63.6 (26.0–91.0)	69.6 (40.0–98.0)	72.6 (34.0–101.0)
Gender, n (%)				
Men	81 (51.6)	108 (54.5)	36 (45.0)	35 (42.2)
Women	76 (48.4)	90 (45.5)	44 (55.0)	48 (57.8)
Race or ethnic group, n (%)				
White	139 (88.5)	173 (87.4)	77 (96.3)	80 (96.4)
Black or African American	9 (5.7)	13 (6.6)	2 (2.5)	2 (2.4)
Hispanic or Latino	5 (3.2)	7 (3.5)	0	0
Other	3 (1.9)	3 (1.5)	0	0
Asian	1 (0.6)	2 (1.0)	0	0
American or Alaskan Native	0	0	1 (1.3)	1 (1.2)
Weight, kg				
Mean (range)	70.1 (29.0–138.0)	70.0 (30.9–135.8)	74.1 (33.5–225.9)	69.4 (36.4–158.8)
Daily dose opioid morphine equivalents, mg/day				
Median (range)	200 (0.0–10,160.0)	190 (0.0–122,560.0)	80 (0.0–633.2)	120 (0.0–4427.0)
P-value[a] vs noncancer	0.0067	0.3041	—	—
Number of laxatives concurrently being used, mean (SD)	2.3 (1.23)	2.0 (1.14)	2.2 (1.04)	2.5 (1.51)
Current pain score, mean (SD)	3.4 (2.49)	3.4 (2.62)	3.9 (3.17)	4.2 (2.83)
Worst pain score, mean (SD)	5.3 (2.79)	5.3 (2.81)	5.3 (2.98)	5.7 (2.72)

ITT = intent to treat; MNTX = methylnaltrexone; SD = standard deviation.
[a]*P*-values based on t-tests to compare cancer patients versus noncancer patients.
The ITT population includes all randomized patients who received ≥1 dose of study drug.

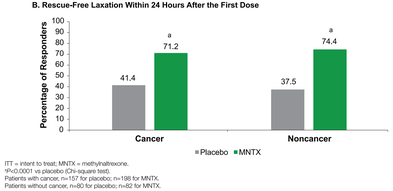
Rescue-Free Laxation Within 4 and 24 Hours

- In both the cancer and noncancer groups, significantly greater percentages of patients treated with MNTX had RFL ≤4 and ≤24 hours after the first dose compared with patients who received placebo (Figures 2A and 2B)

Figure 2. Percentage of Responders With Rescue-Free Laxation (ITT Population)



ITT = intent to treat; MNTX = methylnaltrexone.
[a]*P*<0.0001 vs placebo (Chi-square test).
Patients with cancer, n=157 for placebo; n=198 for MNTX.
Patients without cancer, n=80 for placebo; n=82 for MNTX.

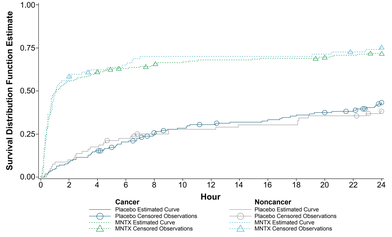


ITT = intent to treat; MNTX = methylnaltrexone.
[a]*P*<0.0001 vs placebo (Chi-square test).
Patients with cancer, n=157 for placebo; n=198 for MNTX.
Patients without cancer, n=80 for placebo; n=82 for MNTX.

Time to First Rescue-Free Laxation

- In both the cancer and noncancer patients, the median time to RFL response after the first dose was significantly shorter with MNTX than with placebo at 4 and 24 hours postdose (Figure 3)

Figure 3. Kaplan-Meier Estimates of Distribution of Time to Rescue-Free Laxation Within 24 Hours After the First Dose of Study Medication for Cancer and Noncancer Patients (ITT Population)

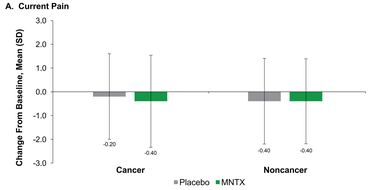


ITT = intent to treat; MNTX = methylnaltrexone.

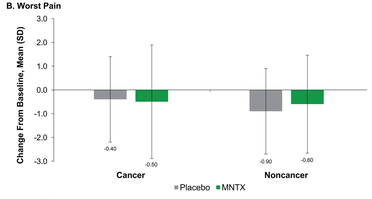
Change From Baseline in Pain Scores

- There were no differences from baseline in pain scores at first assessment in the cancer and noncancer groups. Postbaseline scores for current pain and worst pain were recorded at 4 hours in study 301 and at 24 hours in studies 302 and 4000 (Figures 4A and 4B)

Figure 4. Change From Baseline at 4 Hours or 24 Hours in Pain Scores (ITT Population)



Patients with cancer, n = 138 for placebo; n = 189 for MNTX.
Patients without cancer, n = 76 for placebo; n = 74 for MNTX.



ITT = intent to treat; MNTX = methylnaltrexone; SD = standard deviation.
Patients with cancer, n=137 for placebo; n=186 for MNTX.
Patients without cancer, n=70 for placebo; n=72 for MNTX.

Safety

- Among cancer patients in the safety population who received MNTX (n=241) or placebo (n=157), treatment-emergent adverse events reported in >10% of patients were largely gastrointestinal in nature and included abdominal pain, flatulence, nausea, and vomiting. A similar finding was observed in the noncancer population (Table 2)

Table 2. Number and Percentage of Patients Reporting a Treatment-Emergent Adverse Event That Occurred in at Least 10% of Patients (Safety Population)

	Cancer Patients		Noncancer Patients	
Patients with at least 1 TEAE, n (%)	**Placebo (n = 157)**	**MNTX (n = 241)**	**Placebo (n = 80)**	**MNTX (n = 92)**
Abdominal pain	18 (11.5)	93 (38.6)	11 (13.8)	26 (28.3)
Malignant neoplasm progression	13 (8.3)	65 (27.0)	0	1 (1.1)
Nausea	16 (10.2)	40 (16.6)	7 (8.8)	13 (14.1)
Vomiting	15 (9.6)	36 (15.0)	4 (5.0)	4 (4.3)
Flatulence	7 (4.5)	31 (12.9)	4 (5.0)	13 (14.1)
Pain exacerbated	6 (3.8)	25 (10.4)	1 (1.3)	7 (7.6)
Confusional state	9 (5.7)	25 (10.4)	2 (2.5)	8 (8.7)
Sweating increased	3 (1.9)	25 (10.4)	0	4 (4.3)

MNTX = methylnaltrexone; TEAE = treatment-emergent adverse event.

CONCLUSIONS

- **In this post hoc analysis of 3 trials, MNTX effectively promoted RFL within 4 and 24 hours of dosing and also reduced time to RFL in advanced-illness patients with and without active cancer**
  - **This occurred even though cancer patients were taking higher opioid doses at baseline**
  - **There were no differences in the number of laxatives used**
  - **There were no changes in pain scores after the first assessment**
- **Use of MNTX afforded patients relief of constipation after the first dose without compromising opioid analgesia**

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